UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: July 7, 2004

MEMORANDUM

Subject: EPA File Symbol: 264-IEO LIBERTY 280 SL HERBICIDE
DP Barcode: D304388
Decision No.: 343902
PC Codes: 128850 Glufosinate (CAS#77182-82-2)

From: Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

Byron T. Backus
7-7-2004
JCK

To: James Stone/Joanne Miller RM 23
Herbicide Branch
Registration Division (7505C)

Applicant: BAYER CROPSCIENCE LP

FORMULATION DECLARATION FROM LABEL:

Active Ingredient:	% by wt.
Glufosinate-ammonium (CAS #77182-82-2)	24.5%
Inert Ingredients:	75.5%
Total:	100.00%

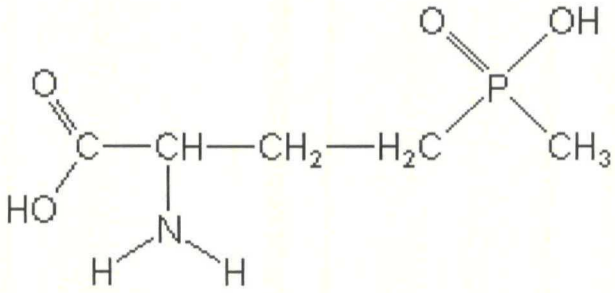
ACTION REQUESTED:

The Risk Manager requests:

"Review acute studies submitted to support application for registration."

BACKGROUND:

The structure of glufosinate (CAS 51276-47-2; an organophosphorus herbicide) is given below:



In this formulation glufosinate is present as the ammonium salt (CAS 77182-82-2).

This package includes an acute oral LD_{50} study (rat, acute toxic class method, MRID 46279002); acute dermal LD_{50} study (rat; MRID 46279003); inhalation LC_{50} study (rat; MRID 46279004); primary eye irritation study (rabbit; MRID 46279005); primary dermal irritation study (rabbit; MRID 46279006); and dermal sensitization study (guinea pig; MRID46279007). All studies were conducted at Bayer HealthCare AG, 42096 Wuppertal, Germany. All studies were conducted on AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid with a specific gravity of about 1.15 g/mL, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate (ammonium salt).

RECOMMENDATIONS:

1. The six acute toxicity studies have been reviewed and classified as acceptable.

2. Based on the results of the acute toxicity studies, the following is the acute toxicity profile for EPA File Symbol: 264-IEO [LIBERTY 280 SL HERBICIDE]. The signal

word of the product is WARNING, based on dermal toxicity and eye irritation potential.

Study Type	Tox. Cat.	Classification & MRID #
Acute Oral LD_{50} (rat)	III	Acceptable (#46279002)
Acute Dermal LD_{50} (rat)	II	Acceptable (#46279003)
Acute Inhalation LC_{50} (rat)	IV	Acceptable (#46279004)
Primary Eye Irritation (rabbit)	II	Acceptable (#46279005)
Primary Dermal Irritation (rabbit)	IV	Acceptable (#46279006)
Dermal Sensitization (guinea pig)	Positive	Acceptable (#46279007)

3. Based on the acute toxicity profile and proposed uses, the following is the precautionary labeling for this product, as obtained from the Label Review System:

PRODUCT ID #: **000264-00829**

PRODUCT NAME: LIBERTY 280 SL HERBICIDE

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **WARNING**

SPANISH SIGNAL WORD: AVISO
Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

Hazards to Humans and Domestic Animals:

May be fatal if absorbed through skin. Causes substantial but temporary eye injury. Harmful if swallowed. Do not get in eyes, on skin, or on clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, socks, chemical-resistant footwear, and chemical-resistant gloves (such as Barrier Laminate, Butyl Rubber, Nitrile Rubber, Neoprene Rubber, Polyvinyl Chloride (PVC), Viton, Selection Category C). Remove and wash contaminated clothing before reuse. Wear protective eyewear (goggles, face shield, or safety glasses).

Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Follow the manufacturer\'s instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry. For overhead exposure wear chemical-resistant headgear. When cleaning equipment wear a chemical-resistant apron.

First Aid:

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable: - technical information on symptomatology; - use of supportive treatments to maintain life functions; - medicine that will counteract the specific physiological effects of the pesticide; - company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Byron T. Backus, Ph.D. **Date:** July 1, 2004
Risk Manager (EPA): 23

STUDY TYPE: Acute Oral Toxicity - Wistar Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL (% a.i.): AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate [Ammonium 2-amino-4-(hydroxymethylphophinyl) butanoate; CAS#77182-82-2]. Described as a brown liquid.

SYNONYMS: The test material description is consistent with the proposed product 264-IEO Liberty 280 SL Herbicide (label declaration of 264-IEO: Glufosinate-ammonium (PC Code 128850; CAS# 77182-82-2) 24.5%; Inert ingredients: 75.5%). According to the proposed label there are 2.34 lbs of active per U.S. gallon, so there would be 9.551 lbs of formulated product in a gallon (indicating a specific gravity of 1.145).

CITATION: Schüngel, M. (2004). AE F039866 00 SL25 S7 Acute Toxicity in the rat after oral administration. Bayer HealthCare AG, D-42096 Wuppertal. Study No.: T 0073884; Activity ID: TXGLY001. Study Completion Date: 15 April 2004. MRID 46279002. Unpublished.

SPONSOR: Bayer Cropscience LP

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46279002), conducted using the acute toxic class method, AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, was administered by oral gavage to groups of 3 fasted (16-24 hr) female Wistar (strain HsdCpb:Wu) rats (weights at dosing: 162-178 g, corresponding to an approximate age of 10-11 weeks; source: Harlan Winkelmann GmbH, D-33178 Borchen). Doses were 2000 mg/kg, 300 mg/kg, and (again) 300 mg/kg; the test material was diluted with demineralized water and administered at a constant dose volume of 10 mL/kg.

On the day of dosage rats were observed several times and then at least once daily for the remainder of the 14-day observation period for mortality and signs of clinical toxicity.. Individual body weights were recorded just prior to dosing (Day 1) and on days 8 and 15.

For the six rats dosed at 300 mg/kg there was no mortality and no signs of toxicity were observed. All gained weight in the period from day 1 to 8 and again from day 8 to 15. Two of the 3 rats dosed at 2000 mg/kg died (deaths on days 3 and 4). Symptoms observed in one or more rats at this dose included piloerection, uncoordinated gait, spasmodic state, hunched posture, increased salivation, narrowed palpebral fissure and "abdominal position." The one survivor (with no symptoms after day 4) at this dosage level had normal weight gains for days 1-8 and 8-15. There were no gross pathological findings for either the rats which died or those which survived to terminal sacrifice.

LD_{50} (Females) cut-off: 1000 mg/kg ["according to OECD Guideline 423."]

AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, is in EPA toxicity category III in terms of oral exposure based on the rat female LD_{50} cut-off value of 1000 mg/kg ["according to OECD Guideline 423."]

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 6), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
300	-	0/6	-
2000	-	2/3	-

Statistics - Not used to compute the oral LD_{50}. From p. 8 of MRID 46279002: "According to OECD guideline 423 the LD50 cut-off of AE F039866 00 SL25 is 1000 mg/kg body weight (Category 4 of the Globally Harmonized Classification System).

A. Mortality - As noted in the table above.

B. Clinical observations - No signs of toxicity were observed in the 6 rats dosed at 300 mg/kg. All gained weight in the period from day 1 to 8 and again from day 8 to 15. Two of the 3 rats dosed at 2000 mg/kg died (deaths on days 3 and 4). Symptoms observed in one or more rats at this dose included piloerection, uncoordinated gait, spasmodic state, hunched posture, increased salivation, narrowed palpebral fissure and "abdominal position." The one survivor (no symptoms after day 4) at this dosage level had normal weight gains for days 1-8 and 8-15.

C. Gross Necropsy - There were no gross pathological findings for either the rats which died or those which survived to terminal sacrifice.

D. Reviewer's Conclusions: The study is acceptable. Based on the LD_{50} (Females) cut-off of 1000 mg/kg ["according to OECD Guideline 423"] AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, is in EPA Toxicity Category III in terms of oral toxicity.

E. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** July 1, 2004
Risk Manager (EPA): 23

STUDY TYPE: Acute Dermal Toxicity - Wistar rats - OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate [Ammonium 2-amino-4-(hydroxymethylphophinyl) butanoate; CAS#77182-82-2]. Described as a brown liquid.

SYNONYMS: The test material description is consistent with the proposed product 264-IEO Liberty 280 SL Herbicide (label declaration of 264-IEO: Glufosinate-ammonium (PC Code 128850; CAS# 77182-82-2) 24.5%; Inert ingredients: 75.5%). According to the proposed label there are 2.34 lbs of active per U.S. gallon, so there would be 9.551 lbs of formulated product in a gallon (indicating a specific gravity of 1.145).

CITATION: Schüngel, M. (2004). AE F039866 00 SL25 S7 Acute Toxicity in the rat after dermal application. Bayer HealthCare AG, D-42096 Wuppertal. Study No.: T 0073885; Activity ID: TXGLY001. Study Completion Date: 5 April 2004. MRID 46279003. Unpublished.

SPONSOR: Bayer Cropscience LP

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID #46279003), groups (5M and/or 5F) of Wistar (strain: HsdCpb:Wu) rats (source: Harlan Winkelmann GmbH, D-33178 Borchen; Males: 238-273 g; Females: 206-226 g; 9-13 weeks old) were dermally exposed (approximately 10% of body surface) for 24 hrs to 160 (females only), 400, 1000, or 4000 mg/kg of undiluted AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate. The test material was covered with a taped gauze dressing which was covered with a "Lomir biomedical Inc. rat jacket."

Rats were observed several times after application on day 1 and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing (day 1) and on days 8 and 15.

There was no mortality among the five females dosed at 160 mg/kg. At 400 mg/kg 0/5 males and 2/5 females died; at 1000 mg/kg 2/5 males and 3/5 females died, and at 4000 mg/kg 5/5 males and 5/5 females died. Symptoms at 160 mg/kg were limited to dermal effects. At 400 mg/kg there were sunken flanks, decreased motility, decreased reactivity, temporary increased motility, uncoordinated gait, lateral position, spasmodic state, head bent back, high legged gait, hunched posture, tachypnea, labored breathing and narrowed palpebral fissure. The treatment area was partly reddened, there was formation of scale, encrustation and swelling. At 1000 mg/kg and 4000 mg/kg there were similar findings. Deaths at 400-1000 mg/kg occurred from day 3 to day 7; those at 4000 mg/kg occurred by day 2. Survivors had generally recovered by day 12.

Most (4/5) of the females exposed to 160 mg/kg gained weight in the period from day 1-8, and all gained weight from day 8-15. Most (4/5) males dosed at 400 mg/kg also gained weight from day 1-8, but only 1/3 of the female survivors from this dose group gained weight during this period [one fell from 216 g on day 1 to 168 g on day 8, but then recovered to 229 g on day 15]. At 1000 mg/kg 3/3 male survivors lost weight from day 1 to 8, as did 1/ 2 female survivors.

Gross pathology findings in some of the rats which died included discoloration of the lung or liver and spleen diminished in size, although most of the rats which died showed no findings other than skin reddening at the application site. There were no pathological findings in rats which survived to terminal sacrifice.

Dermal LD_{50} Males = 1400 mg/kg
Females = 800 mg/kg

Based on the female LD_{50} = 800 mg/kg, AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.14) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, is in EPA Toxicity Category II in terms of dermal toxicity.

This acute dermal study is classified as acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 16), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
160	-	0/5	-
400	0/5	2/5	2/10
1000	2/5	3/5	5/10
4000	5/5	5/5	10/10

Statistics - From p. 18 of MRID 46279003: "The LD50 value was calculated with the aid of a software program according to Spearman, Kärber (D.J. Finey; Statistical method in biological assay, 2nd Edition, Griffin, London, 524-530; 1971). The algorithm was taken from L. Sachs (Angewandte Statistik, 6th Edition, 1984, pp. 178 ff.). Because the interval to the highest dose is not arranged in geometrical hierarchy the results are considered to be approximations."

A. Mortality - As noted in the table above.

B. Clinical observations - Symptoms at 160 mg/kg were limited to dermal effects. At 400 mg/kg there were sunken flanks, decreased motility, decreased reactivity, temporary increased motility, uncoordinated gait, lateral position, spasmodic state, head bent back, high legged gait, hunched posture, tachypnea, labored breathing and narrowed palpebral fissure. The treatment area was partly reddened, there was formation of scale, encrustation and swelling. At 1000 mg/kg and 4000 mg/kg there were similar findings. Deaths at 400-1000 mg/kg occurred from day 3 to day 7; those at 4000 mg/kg occurred by day 2. Survivors had generally recovered by day 12.

Most (4/5) of the females exposed to 160 mg/kg gained weight in the period from day 1-8, and all gained weight from day 8-15. Most (4/5) males dosed at 400 mg/kg also gained weight from day 1-8, but only 1/3 of the female survivors from this dose group gained weight during this period [one fell from 216 g on day 1 to 168 g on day 8, but then recovered to 229 g on day 15]. At 1000 mg/kg 3/3 male survivors lost weight from day 1 to 8, as did 1/ 2 female survivors.

C. Gross Necropsy - Gross pathology findings in some of the rats which died included discoloration of the lung or liver and spleen diminished in size, although most of the rats which died showed no findings other than skin reddening at the application site. There were no pathological findings in rats which survived to terminal sacrifice.

D. Reviewer's Conclusions: The study is acceptable. Based on the female rat LD_{50} of 800 mg/kg, AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.14) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, is in EPA Toxicity Category II in terms of dermal toxicity.

E. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** July 2, 2004
Risk Manager (EPA): 23

STUDY TYPE: Acute Inhalation Toxicity - Wistar rats; OPPTS 870.1200; OECD 403

TEST MATERIAL (% a.i.): AE F039866 00 SL25 S7, Batch no. O3 DAL 002 PP098-5, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate [Ammonium 2-amino-4-(hydroxymethylphophinyl) butanoate; CAS#77182-82-2]. Described as a brown liquid.

SYNONYMS: The test material description is consistent with the proposed product 264-IEO Liberty 280 SL Herbicide (label declaration of 264-IEO: Glufosinate-ammonium (PC Code 128850; CAS# 77182-82-2) 24.5%; Inert ingredients: 75.5%). According to the proposed label there are 2.34 lbs of active per U.S. gallon, so there would be 9.551 lbs of formulated product in a gallon (indicating a specific gravity of 1.145).

CITATION: Jiirgen, P. (2004). AE F039866 00 SL25 S7 Study on Acute Inhalation Toxicity in Rats after oral administration. Bayer HealthCare AG, D-42096 Wuppertal. Study No.: T9073874; PSI Activity: TXGLY001. Study Completion Date: 29 April 2004. MRID 46279004. Unpublished.

SPONSOR: Bayer Cropscience LP

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46279004), a group (5/sex) of young adult (approximately 2 months old) SPF-bred Wistar rats (strain: Hsd Cpb:WU (SPF); source: Harlan-Winkelmann GmbH, Borchen, Germany; River Deutschland GmbH, D-97633 Sulzfeld, Germany; exposed Males: 196-210 g; exposed Females: 169-193 g) were exposed (nose only) for 4 hours to aerosolized AE F039866 00 SL25 S7, Batch no. O3 DAL 002 PP098-5, a dark brown liquid containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate. The concentration of test material was measured gravimetrically 4 times during the exposure period. After correcting for volatile constituents, the mean gravimetric concentration was 2.121 mg/L and the nominal concentration was 13.992 mg/L. The MMAD (measured 2 times during exposure) was 2.4 µm with a GSD of 2.11, and 62% of the aerosol mass was <3 µm. Rats were observed for 14 days after exposure. The results from a control study using group of 5M & 5F Wistar rats which were exposed to air only for 4 hours were used for comparison. Rectal temperatures were measured within ½ hour of the end of exposure using a digital thermometer and a rectal probe for rats. Rats were weighed immediately before exposure (day 0) and on days 3, 7 and 14.

One male exposed to the test material died on day 1. Signs of toxicity in both sexes included bradypnea, labored breathing pattern, breathing sounds, ungroomed haircoat, piloerection, tremor, limp, elevated tail, opisthotonus, high-legged gait, posture-head abnormal, squatting, fasciculations, pallor, cyanosis, emaciation, reduced motility, serous nasal discharge, reddened nose, red encrustations on nose, stridor, red encrustations on muzzle and/or nostrils, ptosis, blepharospasm, mydriasis, miosis and choreoathetosis. Touching of the animals elicited the

following: myoklonic jerks, increased motility, excitement, aggressiveness, vocalization, abnormal digging/preening activities, abnormal behavior and exaggerated reactions. A battery of reflex measurements was made on the first exposure day. Rats which had been exposed to the test material showed increased grip strength (vertical and horizontal) and increased tonus. They showed a bizarre/violent reaction, with or without vocalization, to startle reflexes (sound and touch). Their tail-pinch response was to turn immediately towards the site with an attempt to bite. It was not possible to perform righting response measurements on these rats because of their aggressiveness. Most symptoms were gone by day 10, although some (breathing sounds, exaggerated reaction) persisted in a few animals through day 13.

Following exposure, the mean rectal temperature of exposed males was 27.6°C; for controls it was 37.9°C. The mean rectal temperature of exposed females was 31.4°C; for controls it was 38.5°C.

Body weights of all rats dropped dramatically between day 0 and day 3; the mean weight of the 4 males which survived was 203.5 (S.D. 6.6) g on day 0; on day 3 it was 157.8 (S.D. 27.8) g; for females it was 179.8 (S.D. 9.3) g on day 0 and 151.2 (19.8 g). All survivors gained weight between days 0 and 14, but the mean body weight of exposed males was significantly lower (p reported = 0.0075) than controls on day 14 (221.8 g vs. 275.6 g).

Gross necropsy of the dead male showed dark-red marbled firm consistency lung, bloated stomach, yellow-mucous content of small intestine, light-colored spleen and bilaterally light marbled kidneys. Post sacrifice gross necropsy of survivors showed no observable findings.

LC_{50} Males > 2.121 mg/L (1/5M died following exposure to this concentration).
LC_{50} Females > 2.121 mg/L (0/5F died following exposure to this concentration).
LC_{50} Combined > 2.121 mg/L (1/10 died).

Toxicity based on male, female & combined LC_{50} (>2.121 mg/L) is EPA Toxicity Category IV.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 6), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Mean Conc. (Gravimetric; mg/L)	MMAD µm	GSD	Mortality/Number Tested		
				Males	Females	Combined
13.992	2.121	2.4	2.11	1/5	0/5	1/10

Test Atmosphere / Chamber Description:

Chamber Volume:	**3.8 L**
Mean Airflow:	**14 LPM**
Mean Temperature:	**20.8°C**
Mean Relative Humidity:	**64.7%**
Time to 99% Equilibrium:	**"Within the first minute of exposure."**

Test atmosphere concentration: The concentration of test material was measured gravimetrically 4 times during the exposure period. After correcting for volatile constituents, the mean gravimetric concentration was 2.121 mg/L and the nominal concentration was 13.992 mg/L.

Particle size determination: The MMAD (measured 2 times during exposure) was 2.4 µm with a GSD of 2.11, and 62% of the aerosol mass was <3 µm.

Statistics - It was not necessary to use a statistical method to calculate an LC_{50} value. From p. 18 for calculation of Geometric Standard Deviation (GSD): "Refer to the log probability graph used to calculate the Mass Median Aerodynamic Diameter. Provided that the line is a good fit to the data, the size distribution is log normal, and the calculation of the Geometric Standard Deviation is appropriate. Note that particle size at which the line crosses the 84.1% mark. Note the particle size at which the line crosses the 50% mark and calculate as follows: GSD = 84.1% mark/50% mark.

A. **Mortality** - as noted in the table above one exposed male was found dead on Day 1.

B. **Clinical observations** - Signs of toxicity in both sexes included bradypnea, labored breathing pattern, breathing sounds, ungroomed haircoat, piloerection, tremor, limp, elevated tail, opisthotonus, high-legged gait, posture-head abnormal, squatting, fasciculations, pallor, cyanosis, emaciation, reduced motility, serous nasal discharge, reddened nose, red encrustations on nose, stridor, red encrustations on muzzle and/or nostrils, ptosis, blepharospasm, mydriasis, miosis and choreoathetosis. Touching of the animals elicited the following: myoklonic jerks, increased motility, excitement, aggressiveness, vocalization, abnormal digging/preening activities, abnormal behavior and exaggerated reactions. A battery of reflex measurements was made on the first exposure day. Rats which had been exposed to the test material showed increased grip strength (vertical and horizontal) and increased tonus. They showed a bizarre/violent reaction, with or without vocalization, to startle reflexes (sound and touch). Their tail-pinch response was to turn immediately towards the site with an attempt to bite. It was not possible to perform righting response measurements on these rats because of their aggressiveness. Most symptoms were gone by day 10, although some (breathing sounds, exaggerated reaction) persisted in a few animals through day 13.

Following exposure, the mean rectal temperature of exposed males was 27.6°C; for controls it was 37.9°C. The mean rectal temperature of exposed females was 31.4°C; for controls it was 38.5°C.

Body weights of all rats dropped dramatically between day 0 and day 3; the mean weight of the 4 males which survived was 203.5 (S.D. 6.6) g on day 0; on day 3 it was 157.8 (S.D. 27.8) g; for females it was 179.8 (S.D. 9.3) g on day 0 and 151.2 (19.8 g). All survivors gained weight between days 0 and 14, but the mean body weight of exposed males was significantly lower (p reported = 0.0075) than controls on day 14 (221.8 g vs. 275.6 g).

C. Gross Necropsy - Gross necropsy of the dead male showed dark-red marbled firm consistency lung, bloated stomach, yellow-mucous content of small intestine, light-colored spleen and bilaterally light marbled kidneys. Post sacrifice gross necropsy of survivors showed no observable findings.

D. Reviewer's Conclusions: The results of the study demonstrate an LC_{50} value >2 mg/L for aerosolized AE F039866 00 SL25 S7, Batch no. O3 DAL 002 PP098-5, a dark brown liquid containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate. This defines a toxicity category IV classification by the inhalation exposure route.

Reviewer: Byron T. Backus, Ph.D. **Date:** July 6, 2004
Risk Manager (EPA): 23

STUDY TYPE: Primary Eye Irritation - NZW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL (% a.i.): AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate [Ammonium 2-amino-4-(hydroxymethylphophinyl) butanoate; CAS#77182-82-2]. Described as a brown liquid.

SYNONYMS: The test material description is consistent with the proposed product 264-IEO Liberty 280 SL Herbicide (label declaration of 264-IEO: Glufosinate-ammonium (PC Code 128850; CAS# 77182-82-2) 24.5%; Inert ingredients: 75.5%). According to the proposed label there are 2.34 lbs of active per U.S. gallon, so there would be 9.551 lbs of formulated product in a gallon (indicating a specific gravity of 1.145).

CITATION: Schüngel, M. (2004). AE F039866 00 SL25 S7 Acute Eye Irritation/Corrosion on Rabbits. Bayer HealthCare AG, 42096 Wuppertal. Study No.: T 4073761; Activity ID: TXGLY001. Study Completion Date: 13 April 2004. MRID 46279005. Unpublished.

SPONSOR: Bayer Cropscience LP

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46279005), 0.1 mL of undiluted AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, was instilled into the conjunctival sac of one eye of each of 3 adult female New Zealand White Rabbits (strain: Crl:KBL(NZW)BR; weights: 2972 - 3137 g; ages: 5-6 months; source: Charles River, Kisslegg, Germany). The rabbits were observed for up to 21 days after instillation, with scoring (if appropriate) at 1, 24, 48 and 72 hours, and at 7, 14 and 21 days.

Corneal opacity was seen in all 3 eyes. It had cleared in 1/3 by day 14 and in another rabbit by day 21. The third rabbit was found dead on day 5. "Because the scores for this rabbit at 72 hours were similar to findings in the other two animals, it was determined that no additional animals would be treated." An iridial score of "1" was observed for one eye on days 7 and 14.; all rabbits were positive for conjunctival redness and chemosis at 72 hours, which had cleared in both survivors by day 14.

In this study, AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, is in EPA toxicity category II based on the persistence of corneal opacity in 2/2 eyes at 7 days which subsequently cleared by day 21.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 7), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested						
	1 hr	24 hrs	48 hrs	72 hrs	day 7[1]	day 14[1]	day 21[1]
Corneal Opacity[2]	3/3	3/3	3/3	3/3	2/2	1/2	0/2
Iritis	0/3	0/3	0/3	0/3	1/2	1/2	0/2
Conjunctivae:							
Redness[3]	3/3	3/3	3/3	3/3	1/2	0/2	0/2
Chemosis[3]	2/3	1/3	3/3	3/3	0/2	0/2	0/3
Discharge[3]	3/3	0/3	0/3	0/3	0/2	0/2	0/2

[1]One rabbit was found dead on day 5.
[2]Fluorescein staining was used on several occasions (including at 24, 48 & 72 hrs) to evaluate the extent or verify the absence of corneal opacity.
[3]Score of 2 or more considered positive

A. Observations - Corneal opacity was seen in all 3 eyes. It had cleared in 1/3 by day 14 and in another rabbit by day 21. The third rabbit was found dead on day 5. "Because the scores for this rabbit at 72 hours were similar to findings in the other two animals, it was determined that no additional animals would be treated." An iridial score of "1" was observed for one eye on days 7 and 14.; all rabbits were positive for conjunctival redness and chemosis at 72 hours, which had cleared in both survivors by day 14.

B. Reviewer's Conclusions: The study adequately defines a Toxicity Category II hazard potential in terms of eye exposure for AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate.

C. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** July 6, 2004
Risk Manager (EPA): 23

STUDY TYPE: Primary Dermal Irritation - NZW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL (% a.i.): AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate [Ammonium 2-amino-4-(hydroxymethylphophinyl) butanoate; CAS#77182-82-2]. Described as a brown liquid.

SYNONYMS: The test material description is consistent with the proposed product 264-IEO Liberty 280 SL Herbicide (label declaration of 264-IEO: Glufosinate-ammonium (PC Code 128850; CAS# 77182-82-2) 24.5%; Inert ingredients: 75.5%). According to the proposed label *there are 2.34 lbs of active per U.S. gallon, so there would be 9.551 lbs of formulated product in* a gallon (indicating a specific gravity of 1.145).

CITATION: Schüngel, M. (2004). AE F039866 00 SL25 S7 Acute Skin Irritation/Corrosion on Rabbits. Bayer HealthCare AG, 42096 Wuppertal. Study No.: T 3073760; Activity ID: TXGLY001. Study Completion Date: 7 April 2004. MRID 46279006. Unpublished.

SPONSOR: Bayer Cropscience LP

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46279006), aliquots of 0.5 mL undiluted AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, were applied to dermal sites on each of 3 female adult New Zealand White (strain: Crl:KBL(NZW)BR; weights: 2763 - 3339 g; ages: 6-7 months; source: Charles River, Kisslegg, Germany) albino rabbits, with 4-hour exposure on a 2.5 cm x 2.5 cm area of skin.

After 4 hours, the dressing and patch were removed. The test sites were scored (Draize) at 1, 24, 48 and 72 hrs. Two sites that had scored "1" for erythema were further scored on day 7.

All sites scored zero for edema at 1, 24, 48 and 72 hours. Two sites scored "1" for erythema at 24, 48 and 72 hours, but zero for erythema on day 7. The PII = 0.50.

In this study, AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate, is in EPA Toxicity Category IV for dermal irritation effects, based on the PII of 0.50 and lack of significant dermal irritation following 4-hr exposure.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 7), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Reviewer: Byron T. Backus, Ph.D. **Date:** July 6, 2004
Product Manager (EPA): 23

STUDY TYPE: Dermal Sensitization - albino Guinea Pig; OPPTS 870.2600; OECD 406, 429

TEST MATERIAL (% a.i.): AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate [Ammonium 2-amino-4-(hydroxymethylphophinyl) butanoate; CAS#77182-82-2]. Described as a brown liquid.

SYNONYMS: The test material description is consistent with the proposed product 264-IEO Liberty 280 SL Herbicide (label declaration of 264-IEO: Glufosinate-ammonium (PC Code 128850; CAS# 77182-82-2) 24.5%; Inert ingredients: 75.5%). According to the proposed label there are 2.34 lbs of active per U.S. gallon, so there would be 9.551 lbs of formulated product in a gallon (indicating a specific gravity of 1.145).

CITATION: Vohr, H.W. (2004). AE F039866 00 SL25 S7 Study for the Skin Sensitization Effect in Guinea Pigs (Buehler Patch Test). Bayer HealthCare AG, 42096 Wuppertal. Study No.: T 1073047. Study Completion Date: 28 April 2004. MRID 46279007. Unpublished.

SPONSOR: Bayer Cropscience LP

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46279007) with AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active ammonium Glufosinate, 20 female adult SPF-bred Crl:HA guinea pigs (source: Charles River Laboratory Animal Breeders in 88353 Kisslegg, Germany; weights: 341-418 g; ages: 3-4 weeks) were tested using a Buehler protocol. Each received 3 weekly 0.5 mL 6-hr induction exposures to dilutions of the test material (1st & 2nd induction: 50% of the test material in physiological saline; 3rd induction: 12% in physiological saline; in a preliminary range-finding study 2/5 guinea pigs were sacrificed after simultaneous exposure to 3 concentrations -25%, 50% and 100% - of test material). After a two week rest period, the guinea pigs were challenged (6-hr exposure) at a previously unexposed site with 0.5 mL of the 12% dilution of the test material in physiological saline. A control group of 10 female guinea pigs, which had been treated with physiological saline only during the induction period, was similarly challenged.

Challenge application sites were scored at 24 and 48 hrs following removal of the exposure patch.

Following challenge, 7/20 of the previously induced guinea pigs had a positive response at 24 hours and 11/20 were positive at 48 hours. 0/9 controls (1 control animal died) showed a similar response at 24 and/or 48 hours.

The report includes a very short summary from a positive control study conducted with Alpha Hexyl Cinnamic Aldehyde (alpha-HCA), with 30% alpha-HCA in polyethylene (PEG) 400 used for induction treatments and 20% alpha-HCA in PEG-400 for challenge. According to the

summary 84% of the induced guinea pigs had dermal reactions following challenge, while 0% of their controls showed a reaction. This positive control study summary would normally be considered inadequate (one major deficiency: no information is provided as to when it was conducted). However, as the test material was positive a positive control study is not necessary as additional data.

In this study the test material, **AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active ammonium Glufosinate, was shown to be a potential dermal sensitizer.**

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406, 429) in the Guinea pig.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 6), and [No] Data Confidentiality (p. 2) statements were provided.

I. PROCEDURE

A. Induction - Each of 20 female adult SPF-bred Crl:HA guinea pigs (source: Charles River Laboratory Animal Breeders in 88353 Kisslegg, Germany; weights: 341-418 g; ages: 3-4 weeks) were tested using a Buehler protocol. Each received 3 weekly 0.5 mL 6-hr induction exposures to dilutions of the test material (1st & 2nd induction: 50% of the test material in physiological saline; 3rd induction: 12% in physiological saline; in a preliminary range-finding study 2/5 guinea pigs were sacrificed after simultaneous exposure to 3 concentrations -25%, 50% and 100% - of test material).

B. Challenge - Challenge (2 weeks after the last induction treatment) was for 6 hours to 0.5 mL of a 12% dilution of test material in physiological saline.

C. Naive Controls - At the time the 20 previously induced guinea pigs were challenged, 10 previously unexposed (negative control) guinea pigs were similarly challenged.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Following challenge, 7/20 of the previously induced guinea pigs had a positive response at 24 hours and 11/20 had a positive at 48 hours. 0/9 controls (1 control animal died) showed a similar response at 24 and/or 48 hours.

B. Positive control - The report includes a very short summary from a positive control study conducted with Alpha Hexyl Cinnamic Aldehyde (alpha-HCA), with 30% alpha-HCA in polyethylene (PEG) 400 used for induction treatments and 20% alpha-HCA in PEG-400 for challenge. According to the summary 84% of the induced guinea pigs had dermal reactions following challenge, while 0% of their controls showed a reaction. This positive control study summary would normally be considered inadequate (one major deficiency: no information is provided as to when it was conducted). However, as the test material was positive a positive

control study is not necessary as additional data.

C. **Reviewer's Conclusions:** Based on the results of this study **AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active ammonium Glufosinate, was shown to be a potential dermal sensitizer.**

D. **Deficiencies** - Information regarding the positive control study (including the date it was conducted) is inadequate; however, as the test material was positive, we can classify the study as acceptable.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D304388
2. **PC CODES:** 128850 Glufosinate (CAS#77182-82-2)
3. **CURRENT DATE:** July 7, 2004
4. **TEST MATERIAL:** AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate [Ammonium 2-amino-4-(hydroxymethylphophinyl) butanoate; CAS#77182-82-2]. Described as a brown liquid. The test material description is consistent with the proposed product 264-IEO Liberty 280 SL Herbicide (label declaration of 264-IEO: Glufosinate-ammonium (PC Code 128850; CAS# 77182-82-2) 24.5%; Inert ingredients: 75.5%). According to the proposed label there are 2.34 lbs of active per U.S. gallon, so there would be 9.551 lbs of formulated product in a gallon (indicating a specific gravity of about 1.15).

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/ Bayer HealthCare AG Wuppertal Germany/Study No. T 0073884/ 15-APR-2004	46279002	LD_{50}=1000 mg/kg by acute tox class method. 6/6 female Wistar rats dosed at 300 mg/kg survived without showing signs of toxicity. At 2000 mg/kg 2/3 died; symptoms included piloerection, uncoordinated gait, spasmodic state, hunched posture, increased salivation, narrowed palpebral fissure and "abdominal position." The one at this dose was normal after day 4 and had normal weight gains for days 1-8 and 8-15. No gross pathological findings for either the rats which died or those which survived to terminal sacrifice.	III	A
Acute dermal toxicity/rat/ Bayer HealthCare AG Wuppertal Germany/Study No. T 0073885/ 5-APR-2004	46279003	LD_{50} (F) = 800 mg/kg; LD_{50} (M) = 1400 mg/kg. Groups of 5M & 5F Wistar rats were dermally exposed to 160 (F only), 400, 1000 or 4000 mg/kg for 24 hrs. At 160 mg/kg 0/5F died; at 400 mg/kg 0/5M & 2/5F died; at 1000 mg/kg 2/5M & 3/5F died; at 4000 mg/kg 5/5M & 5/5F died. Symptoms at 160 mg/kg were limited to dermal irritation effects. At higher doses there were sunken flanks, decreased motility, decreased reactivity, temporary increased motility, uncoordinated gait, hunched posture, tachypnea & labored breathing. Gross pathology findings in some of rats which died included discoloration of lungs or liver and/or spleen decreased in size, although most only showed dermal effects. No pathological findings in rats surviving to terminal sacrifice.	II	A

Acute inhalation toxicity/rat/Bayer HealthCare AG Wuppertal Germany/Study No. T 9073874/ 29-APR-2004	46279004	LC_{50}> 2.121 mg/L. Nose-only exposure. 1/5M & 0/5F died after exposure to gravimetrically determined *concentration of* 2.121 *mg/L*; MMAD = 2.4 µm with an average GSD of 2.11. Signs of toxicity included bradypnea, labored breathing pattern, breathing sounds, ungroomed haircoat, piloerection, tremor, limp, elevated tail, opisthotonus, high-legged gait, squatting, fasciculations, pallor, cyanosis, emaciation, reduced motility, serous nasal discharge, reddened nose, stridor, ptosis, blepharospasm, mydriasis, misosis and choreoathetosis. Touching of animals elicited myoclonic jerks, excitement, aggressiveness, vocalization, abnormal behavior and exaggerated reactions. Immediately following exposure mean rectal temp. of males was 27.6°C; for controls it was 37.9°C; for exposed females it was 31.4°C and for their controls it was 38.5°C. Body weights of all exposed rats dropped dramatically between day 0 and 3 (mean wts: males: 203.5 g to 157.8; females: 179.8 to 151.2 g). All survivors gained wt between days 0 and 14, but the mean body wt of exposed males was significantly lower than their controls on day 14 (221.8 g vs. 275.6 g). Gross necropsy of dead male showed dark-red marbled firm consistency lung, bloated stomach, yellow-mucous content of stomach, light-colored spleen and light marbled kidneys. Post sacrifice gross necropsy of survivors showed no observable findings.	IV	A
Primary eye irritation/rabbit/ Bayer HealthCare AG Wuppertal Germany/Study No. T 4073761/ 13-APR-2004	46279005	Corneal opacity (described as "degree of density of the cornea grade 1") was seen in 3/3 rabbits at 1-72 hrs. One rabbit died day 5; corneal opacity still present in 2/2 eyes on day 7, in 1 /2 on day 14 and all eyes had cleared by day 21.	II	A
Primary dermal irritation/rabbit/ Bayer HealthCare AG Wuppertal Germany/Study No. T 3073760/ 7-APR-2004	46279006	3 rabbits used; maximum score for erythema = 1; for edema = 0; all sites zero by day 7. PII = 0.50.	IV	A

Dermal sensitization/guinea pig/ Bayer HealthCare AG Wuppertal Germany/Study No. T 1073047/ 28-APR-2004	46279007	3-induction treatment Buehler test. 6-hr induction exposures were 1 week apart; they were to 0.5 mL 50% test material in physiological saline (1st & 2nd) and to 12% in physiological saline (3rd). Challenge was to 0.5 mL 12% test material in physiological saline. 7/20 previously induced female guinea pigs had a positive response at 24 hrs after challenge, and 11/20 were positive at 48 hrs. 0/9 controls (one had died) showed a positive response. Positive control study summary is inadequate (for one thing, no date for this study is given) but since test material was positive we can accept the overall study.	Yes	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**

A. Observations - All sites scored zero for edema at 1, 24, 48 and 72 hours. Two sites scored "1" for erythema at 24, 48 and 72 hours, but zero for erythema on day 7.

B. Results - The PII (average of 1, 24, 48 and 72-hour scores) =0.50. The mean irritation score on day 3 was 0.67 (erythema: 0.67; edema: 0.0).

C. Reviewer's Conclusions - The study adequately demonstrates a Toxicity Category IV hazard potential in terms of dermal irritation for AE F039866 00 SL25 S7, Batch no. 03DAL002P098-5, a brown liquid (specific gravity about 1.15) containing a nominal 280 g/L and an analytically determined 24.3% of the active Glufosinate.

D. Deficiencies - None